3. (Amended) A library according to claim 1, wherein the encoded partially randomised zinc finger comprises [the] a zinc finger of the Zif 268 polypeptide.

19. (Amended) A DNA library [according to claim 1,] consisting of 64 sequences, each sequence comprising a different one of the 64 possible permutations of a DNA triplet, the library being arranged in twelve sublibraries, wherein for any one sub-library one base in the triplet is defined and the other two bases are randomised.

23. (Amended) A kit for making a zinc finger polypeptide for binding to a nucleic acid sequence of interest, comprising: a library of DNA sequences according to claim 1 encoding zinc finger polypeptides [into] in a vector; a vector molecule that accepts one or more sequences from the library; and instructions for use.

32. (Amended) A library according to claim 31, wherein the zinc finger polypeptide is displayed on a viral particle.[.]

Please cancel claims 42-53 and 75-103, without prejudice or disclaimer.

II. REMARKS

Claims 1-74 were indicated as pending and were subject to restriction. As indicated in the attached third preliminary amendment, received at the USPTO on December 19, 2002, claims 54-74 were caceled and claims 75-103 were added. Thus, claims 1-53 and 75-103 were pending prior to examination. Claims 42-53 and 75-103 have been canceled by amendment herein. Accordingly, claims 1-41 are pending. Applicants reserve the right to file one or more continuing applications directed to the subject matter of these claims during the pendency of this application.

Sequence Listing

In view of the foregoing amendments to the "Brief Description of the Drawings," Applicants submit that a new Sequence Listing is not required and request that this objection be withdrawn.

Restriction Requirement

The Office has required election of one of the following allegedly distinct inventions:

Group I (originally patented claims 1-41); drawn to a library of DNA sequences, methods for designing and producing ZFPs, and methods of modifying a nucleic acid of interest, class 536, subclass 23.1 and class 435, subclass 6 and 69.1;

Group II (claims 42-49); drawn to a polypeptide comprising a designed zinc finger polypeptide and at least one functional domain, classified in class 530, subclass 350;

Group III (claims 50-53); drawn to a polynucleotide encoding a polypeptide comprising a designed zinc finger polypeptide, class 536, subclass 23.4; and

Group IV (claims 54-74), drawn to a method of altering expression of a chromosomal gene, class 435, subclass 375.

Group I has been constructively elected for examination. Applicants again note that claims 54-74 (Group IV) were canceled and new claims 75-103 were added in the third preliminary amendment received by the USPTO on December 19, 2002. Applicants submit that claims 75 and 77 are directed to the compositions of Group II; claims 76 and 78 are directed to the compositions of Group III; while claims 79-103 are drawn to methods of Group IV, which appear to be encompassed by claim 14 of Group I. Thus, Applicants request that Group II be redrawn to include claims 75 and 77; Group III be redrawn to include claims 76 and 78; and Group I be redrawn include claims 79-103. Applicants have (on even date herewith) filed two divisional applications directed to the subject matter alleged by the Examiner to fall into Groups II and III, respectively. Applicants reserve the right to file one or more additional continuing applications directed to the subject matter of these claims during the pendency of this application.

Information Disclosure Statement

Applicants acknowledge the Examiner's reminder of their continuing duty under 37 C.F.R. § 1.56 to apprise the Office of material information. An Information Disclosure Statement was submitted pursuant to 37 C.F.R. § 1.97 on February 20, 2003.

Consent of Assignee

Applicants thank Examiner McKelvey for taking the time to discuss the contents of the file with Applicants' undersigned attorney. During this discussion, it was determined that the Office did not have a copy of the signed "reissue application: consent of assignee." Enclosed

herewith is a stamped postcard indicating receipt of the document on December 27, 2001. For the Examiner's convenience, a copy is submitted herewith. Furthermore, Applicants note that ownership of this patent application has changed and a new consent of assignee was filed on November 25, 2002. A copy is also attached hereto. Thus, Applicants fully complied with the requirements of 37 C.F.R. § 1.172.

Original Patent

Submitted herewith is the original patent.

Preliminary Amendment

The Office Action indicates that the preliminary amendment filed December 27, 2001 proposed amendments to the specification that were not in conformance with 37 C.F.R. 1.173(b). (Office Action, page 10). In particular, it was alleged that proper underling of added material and square bracketing of deleted material was not performed. Applicants believe that the amendments made in the third preliminary amendment were in accordance to 37 C.F.R. 1.173 as evidenced by the underlining and square bracketing of the **version showing changes made**. Nevertheless, to expedite prosecution, the same changes are shown in the "amendments" section of this response, thereby obviating this rejection.

Priority

Applicants thank the Examiner for noting the application must contain a claim for priority in the first sentence of the application or in an application data sheet. By amendment herein, the specification now recites the domestic priority claims in the first sentence of the specification.

Informalities

Claims 23-25 and 32 were objected to for containing a grammatical error ("into" instead of "in" in claim 23) and for containing two periods (claim 32). (Office Action, page 11).

Applicants thank the Examiner for the suggested corrections and have incorporated the suggestions by amendment herein. Accordingly, these objections have been obviated.

35 U.S.C. § 112, Second Paragraph

Claim 3 was rejected as allegedly indefinite on the basis that there was no antecedent basis for referring to Zif268 as "the" zinc finger protein. (Office Action, page 11). Applicants have amended the claim here in as suggested by the Examiner. Accordingly, the rejection has been obviated and withdrawal thereof is respectfully requested.

Obviousness-type Double Patenting

Examined claims 1-41 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over the claims 1-26 of U.S. Patent No. 6,013,453. (Office Action, pages 12-13). The Examiner has indicated that a terminal disclaimer may be used to overcome this rejection. (Office Action, page 12). Accordingly, Applicants note that upon indication of allowability of claims 1-41, they will consider preparing and submitting a terminal disclaimer relative to U.S. Patent No. 6,013,453.

III. CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Respectfully submitted,

Date: 26 March 03

By: Dpasternak
Dahna S. Pasternak
Registration No. 41,411
Attorney for Applicant

Cooley Godward LLP
Five Palo Alto Square
3000 El Camino Real
Palo Alto, CA 94306
Tel.: (650) 843-5608
Fax: (650) 857-0663

Version Showing Changes Made to the Specification

The paragraph beginning at column 9, line 5 has been amended as follows:

To the best knowledge of the inventors, design of a zinc finger polypeptide and its successful use in modulation of gene expression (as described below) has never previously been demonstrated. This breakthrough presents numerous possibilities. In particular, zinc finger polypeptides could be designed for therapeutic and/or prophylactic use in regulating the expression of disease-associated genes. For example, zinc finger polypeptides could be used to inhibit the expression of foreign genes (e.g., the genes of bacterial or viral pathogens) in man or animals, or to modify the expression of mutated host genes (such as oncogenes).

The paragraph beginning at column 12, line 34 has been amended as follows:

Colonies were transferred from plates to 200 ml 2xTY/Zn/Tet (2xTY containing 50 μM $Zn(CH3.COO)_2$ and 15 μg/ml tetracycline) and grown overnight. Phage were purified from culture supernatant by two rounds of precipitation using 0.2 volumes of 20% PEG/2.5M NaCl containing 50, μM $Zn(CH3.COO)_2$, and resuspended in zinc finger phage buffer (20 mM HEPES pH7.5, 50 mM NaCl, 1 mM $MgCl_2$ and 50 μM $Zn(CH3.COO)_2$). Streptavidin-coated paramagnetic beads (Dynal) were washed in zinc finger phage buffer and blocked for 1 hour at room temperature with the same buffer made up to 6% in fat-free dried milk (Marvel). Selection of phase was over three rounds: in the first round, beads (1 mg) were saturated with biotinylated oligonucleotide (~80 nM) and then washed prior to phage binding, but in the second and third rounds 1.7 nM oligonucleotide and 5 μg poly dGC (Sigma) were added to the beads with the phage. Binding reactions (1.5 ml) for 1 hour at 15°C. were in zinc finger phage buffer made up to 2% in fat-free dried milk (Marvel) and 1% in Tween 20, and typically containing $5x10^{11}$ phage. Beads were washed 15 times with 1 ml of the same buffer. Phage were eluted by shaking in 0.1M triethylamine [triethylatnine] for 5 min and neutralised with an equal volume of 1M Tris pH7.4. Log phase *E. coli* TG1 in 2xTY were infected with eluted phage for 30 min at 37°C. and plated as described above. Phage titres were determined by plating serial dilutions of the infected bacteria.

The paragraph beginning at column 19, line 62 has been amended as follows:

Flexible flat-bottomed 96-well microtitre plates (Falcon) were coated overnight at 4°C. with streptavidin (0.1 mg/ml in 0.1M $NaHCO_3$ pH8.6, 0.03% NaN_3). Wells were blocked for one hour with PBS/Zn (PBS, 50 μM $Zn(CH3.COO)_2$) containing 2% fat-free dried milk (Marvel), washed 3 times with PBS/Zn containing 0.1% Tween, and another 3 times with PBS/Zn. The "bound" strand of each oligonucleotide library was made synthetically and the other strand extended from a 5'-biotinylated universal primer using

DNA polymerase I (Klenow fragment). Fill-in reactions were added to wells (0.8 pmole DNA library in each) in PBS/Zn for 15 minutes, then washed once with PBS/Zn containing 0.1% Tween, and once again with PBS/Zn. Overnight bacterial cultures each containing a selected zinc finger phage were grown in 2xTY containing 50 mM $Zn(CH3.COO)_2$ and 15 μg/ml tetracycline at 30°C. Culture supernatants containing phage were diluted tenfold by the addition of PBS/Zn containing 2% fat-free dried milk (Marvel), 1% Tween and 20 μg/ml sonicated salmon sperm DNA. Diluted phage solutions (50 μl) were applied to wells and binding allowed to proceed for one hour at 20°C. Unbound phage were removed by washing [D] 5 times with PBS/Zn containing 1% Tween, and then 3 times with PBS/Zn. Bound phage were detected as described previously (Griffiths et [at] al., 1994 EMBO J. [In Press] 13(14):3245-3260), or using HRP-conjugated anti-M13 IgG (Pharmacia), and quantitated using software package SOFT-MAX 2.32 (Molecular Devices Corp).

The paragraph beginning at column 21, line 61 has been amended as follows:

Table 2 summarises frequently observed amino acid-base contacts in interactions of selected zinc fingers with DNA. The given contacts comprise a "syllabic" recognition code for appropriate triplets. Cognate amino acids and their positions in the α-helix are entered in a matrix relating each base to each position of a triplet. Auxiliary amino acids from position +2 can enhance or modulate specificity of amino acids at position -1 and these are listed as pairs. Ser or Thr at position +6 permit Asp +2 of the following finger (denoted Asp ++2) to specify both G and T indirectly, and the pairs are listed. The specificity of Ser +3 for T and Thr +3 for C may be interchangeable in rare instances while Val +3 appears to be consistently ambiguous.

The paragraph beginning at column 29, line 55 has been amended as follows:

Immunofluorescence microscopy of transfected Ba/F3+p190 cells in the absence of IL-3 shows chromatin condensation and nuclear fragmentation into small apoptotic bodies, while the nuclei of Ba/F3+p210 cells remain intact. Northern blots of total cytoplasmic RNA from Ba/F3+p190 cells transiently transfected with the anti-BCR-ABL peptide revealed reduced levels of $p190^{BCR-ABL}$ mRNA relative to untransfected cells. By contrast, similarly transfected Ba/F3+p210 cells showed no decrease in the levels of $p210^{BCR-ABL}$ mRNA [(FIG. 12)]. The blots were performed as follows: 10 mg of total cytoplasmic RNA, from the cells indicated, was glyoxylated and fractionated in 1.4% agarose gels in 10 mM $NaPO_4$ buffer, pH 7.0. After electrophoresis the gel was blotted onto HYBOND-N (Amersham), UV-cross linked and hybridized to an ^{32}P-labelled c-ABL probe. Autoradiography was for 14 h at -70°C. Loading was monitored by reprobing the filters with a mouse [b-acting] β-actin cDNA.